d) Remarks

Reconsideration and allowance of the present application in view of the foregoing amendments and accompanying remarks are respectfully requested.

Claims 1-12 were pending in the subject application. By this Amendment, applicants have amended claims 1, 3, 6, and 9. Accordingly, upon entry of this Amendment, claims 1-12 will be pending and under examination.

Applicants maintain that amended claims 1, 3, 6, and 9 raise no issue of new matter and are fully supported by the specification as filed.

Support for amended claim 1 may be found *inter alia* in the specification, as originally filed, on page 4, lines 5-12. Support for amended claim 3 may be found *inter alia* in the specification, as originally filed, on page 4, line 5-12; and page 16, lines 20-29. Support for amended claim 6 may be found *inter alia* in the specification, as originally filed, on page 4, line 5-12; and page 17, lines 9-33. Support for amended claim 9 may be found *inter alia* in the specification, as originally filed, on page 4, lines 13-21.

Amendments to the claims are being presented in the manner specified in the Notice dated January 31, 2003 entitled "Amendments in a Revised Format Now Permitted."

Claim Rejections - 35 U.S.C. §112

The Examiner stated that claims 1-12 stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for reasons of record and herein below.

The Examiner stated that in response to the rejection of claims 1-12 under 35 U.S.C. §112, first paragraph, as lacking enablement for gene therapy, applicant asserts that the articles cited by the Examiner to evidence the unpredictability of gene therapy are outdated and that at the time the instant application was filed many advances had been made *in vivo* gene therapy. The Examiner stated that applicant further asserts that at the time of filing *in vivo* gene therapy was not unpredictable and cites Wang *et al.*, (2000) *Mol Ther.* 1:154-158, which teaches long-term correction of the bleeding disorder in hemophilia B dogs by injection of a recombinant adeno-associated virus vector encoding canine factor IX under the control of a liver-specific enhancer/promoter, to support this assertion.

The Examiner stated that these arguments have been fully considered but are not found persuasive because the teachings of Wang *et al.*, in the context of the general unpredictability of gene therapy described in the many articles cited in the previous office action, are allegedly not enabling for treatment using the instant method. The Examiner stated that in particular, as stated in the previous office action, "Verma *et al.*, teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma *et al.* [(1997) *Nature*

389:239-242] page 240, column 2). Verma *et al.* further warns that, `.. .the search for such combinations is a case of trial and error for a given type of cell (Verma *et al. supra*, bridging sentence of columns 2-3)" and "Jin *et al.* (1997, *Bioelectrochem Bioenerg.* Vol. 44, No. 1, pages 111-120) teaches that the efficiency of induction is dependent on the type of cells and the source of cells exposed to the electromagnetic fields (page 112, bridging paragraph of the columns)". The Examiner stated that given these teachings, which demonstrate the unpredictability of obtaining therapeutic levels of expression from any given promoter system and the unpredictability of expression obtained using electromagnetic induction in any given cell type, the skilled artisan would not predict a therapeutic effect resulting from a method comprising introducing electromagnetic response elements into a gene promoter and applying an electromagnetic field based on the teachings of Wang *et al.*, which are specifically directed to expression of a therapeutic gene <u>in liver cells using a liver-specific promoter enhancer.</u>

The Examiner then stated that in response to the Examiner's assertion that one of the factors that the art teaches affect efficient gene delivery and sustained gene expression is anti-viral immune responses, applicant cites Rux *et al.*, (2000) *Mol Ther.* 1:18-30 and argues that Rux teaches, "new modified adenoviral vectors have been made which overcome the problem of immune responses." (page 9) The Examiner stated that this argument is not persuasive because it mischaracterizes the teachings of Rux. Rux teaches the X-ray crystal structure of type 5 adenovirus hexon and identifies serotype specific epitopes within the hexon protein. Rux et al., concludes, "[t]he

improved understanding of hexon should greatly facilitate the design of new hexon molecules to produce chimeric adenovirus vectors for use in gene therapy" (second full paragraph in the second column on page 19). The Examiner stated that the statements in Rux *et al.*, regarding designing adenovirus vectors to evade immune responses are merely prophetic and far from overcome the problem of immune responses.

The Examiner also stated that regarding the Examiner's arguments as to the lack of adequate direction provided, applicant asserts that the specification, coupled with the knowledge and level of skill of the art at the time of filing, does enable a method of gene regulation *in vivo* using electromagnetic response elements. The Examiner stated that applicant cites Junkersdorf *et al.* (2000) *Bioelectromagnetics* 21 :100-106, which teaches the effects of electromagnetic fields in the presence of heat shock on the expression of a reporter gene in C *elegans*, as evidence for *in vivo* expression enhanced by electromagnetic fields. The Examiner stated that this argument is not persuasive because the foundation of the Examiner's argument is the unpredictability of obtaining expression at <u>therapeutic</u> levels *in vivo*. The Examiner stated that the teachings of Junkersdorf *et al.*, does not address the unpredictability of therapeutic expression of a nucleic acid molecule. The Examiner stated that applicant also again cites Wang *et al.* as evidence that *in vivo* gene expression can be stable and at a therapeutic level. The Examiner stated, however, for the reasons provided above, the teachings of Wang *et al.* are not enabling for the instant method, which is directed to therapeutic expression using promoter elements and methodology that is dramatically different from those taught by Wang *et al.*

The Examiner stated that in response to the Examiner's statements regarding the level of predictability in the art and amount of experimentation required to practice the invention, applicant again relies on the teachings of Wang *et al.*, and Junkersdorf *et al.*, to support enablement for the claimed method of gene therapy. The Examiner stated that applicant further argues, "it is known that gene therapy can be used to treat many different types of diseases. Therefore, the specification by mentioning gene therapy, inherently means that it is a method of treating any genetic disease, and therefore, there is not a lack of guidance concerning the treatment of any disease using the claimed method of the instant invention" (page 14). The Examiner stated that regarding the cited art, the skilled artisan could not rely on the teachings therein to provide enablement for therapeutic gene expression using the instant claimed method for the reasons provided above. The Examiner stated that regarding the statement that it is known that gene therapy can be used to treat many different types of diseases, the art of record indicates that, as of the filing date of the instant application, gene therapy was effective only in the treatment of hemophilia B in dogs. The Examiner stated, however, for reasons of record, the teachings of the instant application and prior art do not enable the ordinary skilled artisan to use the instant claimed method to treat even that condition. The Examiner stated that although gene therapy could in theory be used to treat a wide range of diseases, the art of record shows that potential has not as yet been realized and, for reasons of record, could not be realized based on the teachings of the prior art and instant disclosure without engaging in undue experimentation. The Examiner, therefore, stated that the claims stand rejected under 35 U.S.C. §112, first paragraph.

In response, applicants assert that prior to the time of filing (January 25, 2001) many advances have been made in *in vivo* gene therapy. Applicants also assert that the articles (Verma, et al, 1997 and Jin, et al, 1997) which the Examiner had cited in support of the Examiner's assertion that *in vivo* gene therapy was unpredictable are outdated, and do not reflect the state of the art, and its predictability, as of the filing date of this application.

In support of applicants' assertion that *in vivo* gene therapy was not unpredictable at the time of filing, applicants submit the following articles listed below.

Applicants submit the abstract by Jindal, et al., "Prevention of diabetes in the NOD mouse by intramuscular injection of recombinant adeno-associated virus containing the preproinsulin II gene," (*Int J Exp Diabetes Res*, 2001:2(2): 129-38), which is attached hereto as **Exhibit A**. Jindal, et al., showed that by using the adeno-associated virus as a gene delivery vehicle, a recombinant vector containing a rat preproinsulin gene was injected into animals. Therapeutic insulin mRNA was detected at the injection site of the treated animals but not the controls for up to fourteen weeks.

Applicants further submit the article by Ye, X., et al.,"Regulated delivery of therapeutic proteins after *in vivo* somatic cell gene transfer," (*Science*, 1999: 283(5398): 88-91), which is attached hereto as **Exhibit B**. Ye, X., et al., showed that by using adeno-associated viral vectors with a cytomegalovirus promoter, stable delivery of therapeutic proteins at a therapeutic level was achieved with medium to long-term success in an *in vivo* somatic gene transfer experiment.

Applicants also submit the article by Edelberg, et al., "Enhancement of murine cardiac chronotropy by the molecular transfer of the human beta2 adrenergic receptor cDNA," (*J Clin Invest*, 1998: 101(2):337-43), which is attached hereto as **Exhibit C**. Edelberg, et al., showed in an *in vivo* gene therapy experiment that through direct gene transfer by injection into mice using a beta actin promoter, the heart rate was increased at a therapeutic level by 40%.

Applicants submit the article by Edelberg, et al., "Molecular enhancement of porcine cardiac chronotropy," (*Heart*, 2001: 86(5):559-62), which is attached hereto as **Exhibit D**. In an *in vivo* gene therapy experiment conducted, Edelberg, et al., showed that after the beta(2) adrenergic receptor construct using a cytomegalovirus promoter was injected into the heart of pigs, the heart rates increased at a therapeutic level on average 50% in the pigs.

Applicants further submit the article by Rosengart, T.K., et al, "Six-month assessment of a phase I trial of angiogenic gene therapy for the treatment of coronary artery disease using direct intramyocardial administration of an adenovirus vector expressing the VEGF121 cDNA," (*Ann Surg*, 1999: 230(4):466-70), which is attached hereto as **Exhibit E**. Rosengart, T.K., et al., showed that after twenty-one patients who had clinically significant coronary artery disease received direct myocardial injection by an adenoviral vector expressing the human vascular endothelial growth factor using a cytomegalovirus promoter, therapeutic angiogenesis was shown greater than or equal to six months in the patients with only few mild to no side effects.

The article by Navarro, V., et al., "Efficient gene transfer and long-term expression in neurons using a recombinant adenovirus with a neuron-specific promoter," (*Gene Ther*, 1999:6(11):1884-92) demonstrated an effective and safe *in vivo* gene therapy experiment using an adenoviral vector that expressed the LacZ reporter gene under the control of the rat neuron-specific enolase promoter. The article showed that gene expression remained stable for months. The authors also stated that the use of a cell-specific promoter resulted in high *in vivo* efficiency and long-term transgene expression. This article is attached hereto as **Exhibit F**.

The article by Park, F., et al., "Therapeutic levels of human factor VIII and IX using HIV4 based lentiviral vectors in mouse liver," (*Blood*, 2000:96(3):1173-6) demonstrated in an *in vivo* gene therapy experiment that by using HIV4 based lentiviral vectors containing an EF1 alpha enhancer/promoter that therapeutic levels of human factor VIII and IX were achieved in mice for eight weeks and longer. This article is attached hereto as **Exhibit G.**

Furthermore, in the article by Kon, O.L., et al., "Naked plasmid-mediated gene transfer to skeletal muscle ameliorates diabetes mellitus," (*J Gene Med*, 1999:1(3):186-94) showed in an *in vivo* gene therapy experiment that by using cytomegalovirus and hsp70 promoter constructs, naked plasmid-mediated gene transfer to skeletal muscle significantly ameliorates diabetes mellitus. This article is attached hereto as **Exhibit H.**

The article by Steiner, M.S. "Antisense c-myc retroviral vector suppresses established human prostate cancer," (*Hum Gen Ther*, 1998:9(5):747-55), demonstrated in an *in vivo* gene therapy

experiment, that by using a mouse mammary tumor virus promoter with a retrovirus, tumor growth reduction was observed at a sustained therapeutic level. This article is attached hereto as **Exhibit I**.

The abstract by Zhonghua, Bing, et al., "Using Hsp70 promoter to regulate target gene expression in tumor," [article in Chinese] (*The First People's Hospital of Shanghai*, 2001:30(3):198-201), showed that gene expression in tumor cells were successfully regulated using heat and an adenoviral construct with a Hsp70 promoter in an *in vivo* gene therapy experiment. The authors concluded that this provides a useful tool for cancer gene therapy using the adenoviral construct with a Hsp70 promoter. This abstract is attached hereto as **Exhibit J.**

Furthermore, applicants submit four articles listed below which show the predictability of expression obtained even by using electromagnetic induction in a given cell.

The article by Madio, D.P. et el., "On the feasibility of MRI-guided focused ultrasound for local induction of gene expression," (*J Magn Reson*, 1998:8(1): 101-4), showed different ranges of hsp70 induction in rats' legs by using a MRI-guided focused ultrasound to investigate the hsp70 promoter as a possible candidate for use in control of gene expression. A temperature increase of 5-8 degrees C in the focal region for 45 minutes led to a differential expression of the hsp70 mRNA between the focal region and the surrounding tissue ranging from a factor of 3 to 67, which could be interpreted as being able to treat certain diseases (e.g. tumors). This article is attached hereto as **Exhibit K.**

The article by Okano, H, and Ohkubo, C. "Modulatory effects of static magnetic fields on blood pressure in rabbits," (*Bioelectromagnetics*, 2001:22(6):408-18), showed that by using static magnetic fields, blood pressure was altered at therapeutic levels in rabbits who had hypertension or hypotension. This article is attached hereto as **Exhibit L.**

The article by Tofani, S. et al., "Static and ELF magnetic fields induce tumor growth inhibition and apoptosis," (*Bioelectromagnetics*, 2001:22(6):419-28), showed that static and low frequency magnetic fields induced tumor growth inhibition in mice at a therapeutic level with no to few mild side effects. This article is attached hereto as **Exhibit M.**

The article by DiCarlo, J.M. et al., "A Simple Experiment to Study Electromagnetic Field Effects: Protection Induced by Short-Term Exposures to 60 Hz Magnetic Fields," (*Bioelectromagnetics*, 1998:19:498-500), showed that by exposing chick embryos with anoxia to electromagnetic fields, the survival rate of the chick embryos exposed to electromagnetic fields was significantly higher than the controls. This article is attached hereto as **Exhibit N.**

Moreover, in response to the Examiner's assertion that gene therapy was unpredictable using a method comprising introducing electromagnetic response elements into a gene promoter and applying an electromagnetic field for therapeutic uses and that the as-filed specification does not provide guidance to one skilled in the art to make and use the claimed methods without undue experiment, applicants assert that the specification, coupled with the knowledge and skill of the art as of the filing

date (as mentioned above), do enable one to make and use the claimed methods without undue experimentation. In support of applicant's assertions, applicants also submit a signed declaration by Dr. Martin Blank attached hereto as **Exhibit 1**. In the declaration, Dr. Blank states that he believes that someone skilled in the art as of the January 25, 2001 filing date, following only the disclosure of the subject application and other information publicly available at that time, could, without undue amount of experimentation, conduct a working *in vivo* experiment to practice the claimed invention of introducing electromagnetic response elements into a gene promoter not having any electromagnetic response elements and applying an electromagnetic field to induce expression to a subject with sustained therapeutic results. Dr. Martin Blank's curriculum vitae is attached hereto as **Exhibit 2**.

Applicants also assert that delivery systems for gene therapy are not deficient and that the art teaches improved gene delivery systems which overcome immune responses for the reasons listed below.

Applicants note the abstracts and articles mentioned above as **Exhibits A-J** which showed that by using delivery systems such as an adeno-associated virus or an adenovirus, medium-term and/or long-term therapeutic gene therapy results were maintained. Applicants also submit the article attached hereto as **Exhibit O**, which states that recombinant adeno-associated virus vectors appear to offer a vehicle for safe, long term therapeutic results without deleterious effects on the host cell and the relative non-immunogenicity of the virus or viral expressed transgenes. (Kapturczak, M.H., et al, "Adeno-associated virus (AAV) as a vehicle for therapeutic gene

delivery: improvements in vector design and viral production enhance potential to prolong graft survival in pancreatic islet cell transplantation for the reversal of type 1 diabetes," (*Curr. Mol. Med*, 2001:1(2):245-58).

Applicants also submit a report by Collateral Therapeutics, Inc (Public release date: December 1, 2001) which stated in a study that they conducted, that *in vivo* reports showed that male reproductive cells (germ cells) were unaffected following intracoronary delivery of an adenoviral vector. The report also says that their positive results "are consistent with other recent studies using different models and routes of administration," Furthermore, the report says, "This study provides significant new information further supporting the safety of the use of the adenovirus as a vehicle to deliver therapeutic genes in man." The report is attached hereto as **Exhibit P**.

In concluding, applicants assert that around the time of filing of the above-identified application, it would not have required undue experimentation for someone skilled in the art to use the claimed methods of introducing electromagnetic response elements into a gene promoter not having any electromagnetic response elements and applying an electromagnetic field to induce gene expression in a subject with sustained therapeutic results. Applicants also assert that gene therapy even to introduce electromagnetic response elements into a gene promoter not having any electromagnetic response elements and applying an electromagnetic field to induce expression to a subject with sustained therapeutic results was not unpredictable because those results could be predicted and obtained with a reasonable

degree of certainty. The Examiner had stated that the skilled artisan would not predict a therapeutic result resulting from a method comprising introducing electromagnetic response elements into a gene promoter and applying an electromagnetic field because Verma et al, (1997) stated that the search for a right promoter combination is a case of trial and error for a given type of cell. The Examiner also cited Jin et al (1997) who stated, "the efficiency of induction is dependent on the type of cells and the source of cells exposed to the electromagnetic fields." From these two articles which were both published in 1997, the Examiner infers that even around the time of filing of the above-identified application some 3-4 years later, the skilled artisan would not predict a therapeutic result resulting from a method comprising introducing electromagnetic response elements into a gene promoter and applying an electromagnetic field to induce gene expression in a subject.

Applicant asserts that back in 1997, however, gene therapy was not unpredictable, but even if it was in 1997, many advances had been made (from 1997 to 2001) which have overcome any alleged unpredictabilities raised by the Examiner. In support of applicants' assertions, applicants have submitted numerous articles and abstracts attached hereto as **Exhibits A-K** which used the correct promoter combination for a given type of cell to create successful therapeutic *in vivo* gene therapy experiments. **Exhibits A-K** also showed that gene therapy can be predictable in treating many different type of diseases. All these articles are much more recent than the article cited by the Examiner (Verma, et al) and more accurately reflect the state of the art and its predictability as of January 2001. Furthermore, some of the articles mentioned used the same

promoter as the claimed invention (e.g. Hsp70). In addition, the articles attached hereto as **Exhibits K-N** demonstrated that obtaining therapeutic electromagnetic induction in a given cell type is predictable. Thus, the skilled artisan would predict with reasonable certainty that a therapeutic effect would result from a method comprising introducing electromagnetic response elements into a gene promoter and applying an electromagnetic field to induce gene expression in a subject. **Exhibits A-J and Exhibits O-P** also demonstrated that there were better delivery systems available at the time of filing of the above-identified application than at the time the articles the Examiner had cited in Paper No. 14. In addition, the declaration by Dr. Blank attached hereto as **Exhibit 1** and the articles and abstracts attached hereto as **Exhibits A-P** show that the subject application would enable one skilled in the art to practice the presently claimed invention as of the January 25, 2001 filing date.

Applicants also point to M.P.E.P. §2164.02 which states that in respect to *in vitro/in vivo* correlation, the Examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. Furthermore, it says:

> "Since the initial burden is on the Examiner to give reasons for the lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model. A rigorous or an invariable exact correlation is not required."

Although the Examiner asserted that in the last Office Action

(Paper No. 12) that many articles were cited showing lack of enablement for the claimed invention, the most recent articles cited were no later then 1997 (Verma, et al, 1997 and Jin, et al 1997). Applicants point out that the Examiner has not shown more recent articles either in Paper No. 12 or Paper No. 14, which applicants have done here. Applicants urge that the Examiner should recognize that gene therapy has significantly advanced from 1997 through 2001. The level of skill in the art in gene therapy is high and the numerous recent articles cited and the declaration show that gene therapy presently claimed would not require undue experimentation, but instead could be implemented with only routine experimentation following the present specification.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these objections.

Claim Rejections - 35 USC § 112, first paragraph (New Grounds for Rejection Necessitated by Amendment)

The Examiner stated that claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that this is a new matter rejection. The Examiner then stated that applicant has amended claims 1 and 8 such that they are directed to a method comprises introducing electromagnetic response elements into a gene promoter in a mammal. The Examiner stated that to support the amendment, applicant points to page 4, lines 5-12 of the originally filed specification. The Examiner stated

that there is, however, no recitation of "a mammal" in the specification and thus the limitation adds new matter. The Examiner stated that in Paper No. 13, page 15, applicant argues that the amended claims are inherently supported by the term "gene therapy" based on the American Society of Gene Therapy (page 15). The Examiner stated that, however, the definition provided does not state that gene therapy is limited to mammals and thus does not support the added limitation.

The Examiner stated that applicant's argument that introducing a construct into an animal is inherent to any method of gene therapy is persuasive, however, and rejection of the claims on the grounds that the lack of an explicitly stated step of introducing the constructs into an animal renders the claims indefinite is withdrawn.

In response, in an attempt to advance prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have amended claims 1 and 9 to delete the term "in a mammal" and replaced this term with "in a subject." Applicants assert that amended claims 1 and 9 are inherently supported by the term "gene therapy" based on the American Society of Gene Therapy, which is attached hereto as **Exhibit Q**. The definition provided by the American Society of Gene Therapy refers to therapeutic genes administered to a patient. Applicant asserts that the word "subject" has the same meaning as the word "patient." For example, both words are not limited to mammals.

Claims 2-8 are dependent on claim 1, either directly or indirectly, and are thus patentable for at least the same reasons that claim 1 is patentable. Claims 10-12 are dependent

on claim 9, and are thus patentable for at least the same reasons that claim 9 is patentable.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Claim Rejections - 35 USC § 112, second paragraph

The Examiner stated that claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that the claims are allegedly indefinite in their recitation of "introducing electromagnetic field response elements into a gene promoter...in a mammal." The Examiner stated that the claim reads as though the electromagnetic field response elements are introduced into a promoter *in vivo*. The Examiner stated that the disclosure suggests, however, that the electromagnetic field response elements are to be introduced into a promoter *in vitro*, and it is the engineered construct that is then introduced into the animal. The Examiner stated that applicant should amend the claim such that the order of the process steps is clearly set forth.

In response, in an attempt to advance prosecution of the subject application, but without conceding the correctness of the Examiner's position, applicants have amended claims 1 and 9 so that the electromagnetic field response elements are introduced into a promoter *in vitro*, and then the construct is introduced in a subject. Claims 2-8 are dependent on claim 1, either

directly or indirectly, and are thus patentable for at least the same reasons that claim 1 is patentable. Claims 10-12 are dependent on claim 9, and are thus patentable for at least the same reasons that claim 9 is patentable.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

In summary, in light of the remarks and amendments made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection set forth in the February 24, 2003 Office Action.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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